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Joan E. Cain Date

Human Papillomavirus Infections in Human Immunodeficiency Virus Infected Women: A Risk Factor Analysis

By

Joan E. Cain
Master of Science

Clinical Research

_____
Kevin Ault, M.D.
Advisor

_____
Henry M. Blumberg, M.D.
Committee Member

_____
John R. Boring, Ph.D.
Committee Member

_____
John E. McGowan, M.D.
Committee Member

Accepted:

_____
Lisa A. Tedesco, Ph.D. Dean of the Graduate School
_____ Date

Human Papillomavirus Infections in Human Immunodeficiency Virus Infected Women: A Risk Factor Analysis

By

Joan E. Cain
M.D., University of Pennsylvania, 2001

Advisor: Kevin Ault, M.D.

An abstract of
A thesis submitted to the Faculty of the Graduate School of Emory University
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ABSTRACT

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By Joan E. Cain

Objective. The aim of this study was to determine the high risk human papillomavirus (HR-HPV) prevalence and specific risk factors for abnormal Papanicolaou (Pap) smear in a human immunodeficiency virus (HIV) infected population. Additionally, the utility of HPV viral load using relative light unit (RLU) readings in predicting cervical disease was assessed.

Methods. This is a cross-sectional study with 569 HIV-infected women who were enrolled from six different cities across the United States. Risk factor analysis was performed using multivariate logistic regression.

Findings. A total of 486 HIV-infected women were included in this analysis. HR-HPV was found in 45% of the population with 25% having an infection with type 16 or 18. For the group as a whole, history of an abnormal Pap smear, CD4 count <200, history of antiretroviral use, presence of HR-HPV regardless of RLU cut-off, and presence of low risk HPV (LR-HPV) were found to be risk factors for an abnormal Pap smear. On subgroup analysis of those co-infected with HR-HPV and HIV, history of antiretroviral use, RLU $\geq$ 20, CD4 count < 200, history of an abnormal Pap smear, and infection with more than one HR-HPV type were found to be risk factors for an abnormal Pap smear. Finally, a strong association between having an abnormal Pap smear and presence of HR-HPV with an RLU $\geq$ 20 (RR=55.2) was found.

Conclusions: This study was able to identify important predictors of having an abnormal Pap smear in HIV-infected women which may help to individualize follow-up and treatment. HPV viral load as measured by RLU was found to be predictive of cervical disease which could prove useful in resource poor areas where further testing is not readily available. Finally, only 25% of those infected with HR-HPV were infected with either 16 or 18. This implies that in HIV-infected women the vaccine subtypes may need to be broadened.

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Table of Contents

INTRODUCTION

HPV is a necessary, but not sufficient cause of cervical cancer worldwide. HPV related cervical cancer is the second most common cancer in women worldwide (1). Approximately 500,000 new cases of cervical cancer and 250,000 deaths related to cervical cancer occur each year (2). Eighty percent of the new cases of cervical cancer occur in the developing world. This is likely due to poor access to medical care which decreases the rate of cervical cancer screening with Pap smears as well as the human immunodeficiency virus (HIV) pandemic. HPV types, 16 and 18, account for about 70% of the cases of HPV-associated cervical cancer in HIV-uninfected women.

In this study, characteristics were assessed for associations with cervical disease in order to identify a subgroup that is most at risk for cervical disease by comparing two groups of HIV-infected women, those with HPV infection and those without. Cervical disease was defined as any abnormality given that published data suggested HIV-infected women with atypical squamous cells of unknown significance (ASC-US) on cytology have a high incidence of dysplasia on subsequent colposcopic examination (3). Additionally, the utility of HPV viral load using relative light unit (RLU) readings in predicting cervical disease was also assessed. RLU could potentially be a cheaper option than real time polymerase chain reaction (PCR) for measuring HPV viral load making it more useful in resource-poor areas. If specific risk factors are identified, then this may have practical implications such as increasing surveillance with more frequent Pap testing, more aggressive treatment of low grade or precancerous lesions and implementing high risk HPV testing regardless of Pap result.

BACKGROUND

Several studies have shown that HIV-infected women are at increased risk for developing HPV-associated cervical disease and cancer when compared to their HIV-uninfected counterparts (4). Furthermore, treatment for cervical disease and cancer in HIV-infected women has been found to be more difficult with more frequent recurrences, less tumor responsiveness and more aggressive lesions (5). Because of this, the Infectious Disease Society of America (IDSA) has recommended more aggressive guidelines on detection of cervical disease and cancer in HIV-infected women. They recommend that HIV-infected women undergo Pap testing at initial diagnosis and then every six months for the first year (6). If the Pap smear is normal, then yearly Pap smears are recommended in addition to further work-up for subsequently abnormal Pap smears.

Although we know that HIV-infected women are at increased risk for cervical disease and cancer, not all HIV-infected women with cervical disease go on to develop cervical cancer. This suggests that there is a sub-group at higher risk of developing cervical cancer as compared to the group as a whole. However, we are just now beginning to understand what these high-risk characteristics might be. Additionally, since there is a long latency period prior to the development of cervical cancer, most studies looking at risk factors have focused on risk factors for the development of high grade cervical lesions and used this as a surrogate for risk for development of cervical cancer. In fact, the exact mechanism by which HIV increases the risk of HPV-associated cervical disease, and therefore cancer, is unknown. Hawes, et al, found that the HIV-infected women in their study had increased HPV persistence as compared to their HIV-uninfected counterparts (7). Furthermore, the HPV persistence was associated with development of high grade squamous intraepithelial lesions (HSIL) which are felt to be the lesions which evolve into cervical cancer. From this study it was thought that part of the increased HPV persistence is related to immune status since the HIV-infected women with CD4 counts <500 or

high HIV viral loads were at greater risk for HSIL. This is in conflict with one study by Mbulaiteye, et al, which showed that although there was an increase in the risk for developing cervical cancer among HIV infected women, this risk did not vary by CD4 count (8). Furthermore, the incidence of cervical cancer has not appeared to have declined since the introduction of highly active antiretroviral therapy (9). Given these conflicting results, it is clear that there are other important factors in the pathogenesis of HPV in addition to immunocompromise. It has been suggested that there is interplay between HIV and HPV which leads to HPV persistence independently of CD4 count (4, 7, 10). Other possible contributors could be higher risk behavior seen in HIV-infected women and co-infection with multiple HPV types commonly seen in HIV-infected women (11, 12). It is unclear what role infection with multiple HPV types has in cervical disease/cancer pathogenesis, but Lillo, et al, showed that higher HPV load as measured by the Hybrid Capture 2 index, or RLU, was found in women with high-grade cervical dysplasia. Furthermore, there was a dramatic decrease in the viral load after surgical removal of the lesion.

METHODS

H_0: There are no unique risk factors for an abnormal Pap smear among HIV-infected women.

Study Design: This was a cross-sectional study. Information for this analysis was obtained from the data collected in the HPV Sentinel Surveillance (HSS) study which was a multi-center, national study. Enrollment methods for the HSS study have been published separately (13). Women who were due for screening Pap smears were enrolled from HIV care clinics from January 1, 2003 to December 31, 2005. Data was collected by the investigators through a standardized questionnaire which included demographic and behavioral data as well as data abstracted from the patients' medical charts including Pap smear results. Two cervical specimens were obtained from all enrolled women for HR-HPV DNA testing and typing.

Patients: Inclusion criteria were current age between 18 and 65 years of age and last Pap smear being at least 6 months prior to their visit. Patients were excluded if they had a history of a hysterectomy, treatment on the cervix less than 6 months prior to visit or if they were currently pregnant or menstruating.

Predictor Variables were ethnicity, race, age, history of an abnormal Pap smear, history of treatment on the cervix, site, HIV viral load, CD4 count, current antiretroviral use, current smoker, parity, history of sexually transmitted infection, RLU, number of HR-HPV types, age at coitarche, and number of lifetime male sexual partners. RLU was obtained through the Hybrid Capture 2 test (Digene, Gaithersburg, Maryland) which is a nucleic acid hybridization assay with signal amplification that utilizes microplate chemiluminescent detection.

The outcome variable for the bivariate and multivariate logistic regression was Pap test abnormality. This was defined as atypical squamous cells of unknown significance (ASC-US), atypical squamous cells of unknown significance- cannot exclude high grade squamous intraepithelial lesion (ASC-H), low grade squamous intraepithelial lesion (LSIL), or high grade squamous intraepithelial lesion (HSIL).

Sample Size: Overall, 569 HIV-infected women were enrolled from six different cities- Boston, MA; Baltimore, MD; New Orleans, LA; Denver, CO; Seattle, WA; and Los Angeles, CA.

Analysis: This study was analyzed as a case-control study with the odds ratio as the measure of effect showing the relative odds of exposure. Analyses were performed using SAS v 9.2. The outcome variable for the bivariate and multivariate logistic regression was Pap test abnormality. HR-HPV prevalences were calculated for the group as a whole. Chi-square test was used to determine if there was a statistical association between the baseline characteristics and group assignment. Multivariate logistic regression was used to determine which characteristics were predictive of cervical abnormalities. Variables were selected for the final multivariate model using manual, backward stepwise selection. Model fit was assessed by inclusion of those variables with p-values < 0.05. Co-linearity was evaluated and adjusted for in the final model. Cutoff values for variables such as RLU and CD4 count were based on previously published evidence.

RESULTS

Baseline Population Characteristics (Table 1): A total of 486 HIV-infected women were included in this analysis. Eighty percent of the population was a racial minority, defined as African American, Hispanic, Asian or other non-white, and was 30 years old or older. Fifty-eight percent of the population had a history of an abnormal Pap smear, and 41% of the population had a history of treatment on the cervix. The majority of patients (40%) came from New Orleans. Seventy-nine percent of patients had a CD4 count ≥ 200, but only 41% of patients had an undetectable viral load. Fifty-six percent of the population reported antiretroviral use. Forty-five percent of the patients were current smokers, and 82% of patients reported having at least one pregnancy. Eighty-one percent of the women had an RLU< 20. Thirty-two percent of the patients had cervical abnormalities. Eighteen percent of women had coitarche prior to the age of 14. Eighty-three percent of the women reported having 3 or more male sexual partners.

Baseline HR-HPV Prevalence (Table 1): HR-HPV was found in a total of 219 of the 486 patients or 45% of the HIV-infected population. Forty-eight percent of the African American women were found to have HR-HPV infection. Fifty-seven percent of those less than 30 years of age had HR-HPV infection. Fifty-one percent of those who reported to have a history of abnormal Pap smear and 47% of those reporting a history of treatment on the cervix had HR-HPV infection. Fifty-one percent of those patients who came from New Orleans had HR-HPV infection. Fifty-two percent of women with a HIV viral load ≥ 10,000 and 69% of women with CD4 count <200 had HR-HPV infection. Forty-nine percent of patients who reported any current antiretroviral use had HR-HPV infections. Ninety percent of those with an RLU ≥ 20 and 61% of those with cervical abnormalities had HR-HPV infection. The five most prevalent HR-HPV types, in order of frequency, were 53, 52, 70, 18 and 68. Figure 1 shows the frequency of all the HR-HPV types in those with HR-HPV infection. Figure 2 shows the distribution of HR-HPV

types based on Pap smear result. Among those with a normal Pap smear, the most prevalent HR-HPV type was 53 followed by 70, 52, 18 and then 59. Among those with ASC-US/ASC-H, the most prevalent HR-HPV type was 70 followed by 52, 53, and 68. Among those with LSIL/HSIL, the most prevalent type was 52 followed by 18, 53, 58 and then 70. Forty-four percent of those co-infected with HPV were infected with more than one high risk type. Forty percent of those with coitarche prior to the age of 14 and 45% of women who reported having 3 or more male sexual partners had HR-HPV infection.

Analysis of exposure variables and their association with having an abnormal Pap smear (Table 2): On bivariate analysis, history of an abnormal Pap, history of treatment on the cervix, HIV viral load ≥ 10,000, CD4 count < 200, history of antiretroviral use, HC2 assay positivity, RLU ≥ 20, presence of one or more of the five most prevalent HR-HPV in our population (16, 18, 52, 53, 70), co-infection with multiple HR-HPV types, and more than 2 lifetime male sex partners were all associated with having an abnormal Pap smear. No characteristics were found to be protective against having an abnormal Pap smear.

Assessment of RLU utility: Evaluation of RLU cutoffs with respect to association with abnormal Pap smear (Table 3A) showed that about 44% of women infected with HR-HPV had an abnormal Pap smear when RLU was <20, 80% had an abnormal Pap smear when the RLU was between 20 and 499, and 100% had an abnormal Pap smear when the RLU was ≥ 500.

Furthermore, on stratification based on presence or absence of high or low risk HPV together with RLU cutoffs (Table 3B), there was a statistically significant association between having an abnormal Pap smear and presence of HR-HPV regardless of RLU level and presence of LR-HPV. Of note, there was a much stronger association between having an abnormal Pap smear and presence of HR-HPV with an RLU ≥ 20 (RR=55.2) than the other stratification levels.

Evaluation of risk factors for abnormal Pap smear among HIV-infected women: On multivariate analysis (Table 4A), several risk factors for having an abnormal Pap smear were found to be significant. They were history of an abnormal Pap smear, CD4 count <200, history of antiretroviral use, presence of HR-HPV with RLU < 20, presence of HR-HPV with RLU ≥ 20, and presence of LR-HPV.

Subgroup analysis was done among those with HR-HPV co-infection (Table 4B). On multivariate analysis the variables that were found to be significant risk factors for having an abnormal Pap smear and, therefore, included in the final model were history of antiretroviral use, RLU ≥ 20, CD4 count < 200, history of an abnormal Pap smear, and infection with more than one HR-HPV type. This group was further sub-classified into those with CD4 count <200 or CD4 count ≥ 200. Among those with a HR-HPV co-infection and CD4 count <200 (Table 4C), multivariate analysis showed that history of an abnormal Pap smear and infection with a low risk HPV type were predictive of having an abnormal Pap smear. Finally, considering the population with a CD4 count ≥ 200 (Table 4D), multivariate analysis showed current antiretroviral use, history of an abnormal Pap smear, RLU ≥ 20, and infection with >1 HR-HPV type were predictive of having an abnormal Pap smear.

DISCUSSION

The data collected through the HPV Sentinel Surveillance Study affords an opportunity to obtain epidemiologic data on a cross-section of the HIV-infected population receiving care in the United States. Overall, the characteristics which were found to be associated with HR-HPV infection, overall HR-HPV prevalence (45%) and relatively low prevalence of HR-HPV type 16 or 18 infections (25%) are consistent with other published reports regarding HIV-infected women (11, 12, 14). Therefore, it appears as if our population would be generalizable to other HIV-infected populations throughout the United States.

Additionally, it has been shown previously that HIV-infected women tend to have infections with multiple HR-HPV types. Our study confirmed these findings in that 44% of those with a HR-HPV infection were infected with more than one HR-HPV type. This finding together with the low infection rate with types 16 or 18 questions whether the currently available preventive measures will be applicable to HIV-infected women. The approved vaccine for HR-HPV prevention, Gardasil, only includes types 16 and 18 so the vaccine's efficacy in HIV-infected women is questionable.

Also, we were able to identify important risk factors for developing an abnormal Pap smear. Among the group as a whole, the factors that were found to be significant were consistent with those previously published such as history of an abnormal Pap smear, CD4 count < 200/mm^3, and reported use of antiretroviral (14). However, in our analysis we also evaluated the variable, RLU, and found that it was significantly associated with having an abnormal Pap smear result. Interestingly, although any level of RLU was significant in the group as a whole as well as the two CD4 count stratifications, the degree of RLU appears to confer variable risk as evidenced by the presence of HR-HPV with an RLU $\geq$ 20 having an OR=55.2 whereas presence of HR-HPV with RLU < 20 had an OR=5.28. To our knowledge, this is the first time that RLU is described in a risk factor analysis for HIV-infected women. Even though RLU is essentially measuring the

same viral load as real time PCR (rt-PCR), RLU provides this information in a more cost effective means making this feasible in resource limited areas.

Potential limitations of our study are that this was a prevalence study so longitudinal data were not obtained to further test our predictors of abnormal Pap smears. Along these lines, there is potential for a false risk factor association given the cross-sectional nature of the study. This is likely limited, though, since it was required that patients be excluded if they had history of treatment on their cervix less than 6 months prior to visit. Another possible limitation was that some of our historical data was obtained from questionnaire results which could introduce recall bias. Also, our results were similar to those previously published on HIV-infected women, but since 40% of our population came from New Orleans, this may make our data less generalizable to the general U.S. population. Additionally, our outcome variable was cervical abnormalities and not cervical cancer. Since cervical cancer is the outcome with the most potential for morbidity and mortality, this would be the next obvious study to test the predictors identified. Furthermore, we excluded those with a positive HC2 assay, but negative PCR for HR-HPV. This could have excluded those with a true HR-HPV infection. Finally, when looking at the subgroup analysis on those HIV-infected patients with HR-HPV co-infection and a CD4 count <200, the patient numbers were small which could have lead to inaccurate risk factor assessment results for this subgroup.

In conclusion, this study was able to identify important predictors of having an abnormal Pap smear in HIV-infected women. Using this model, a subgroup of women most at risk for cervical abnormalities was identified. This could be used to recognize those who may need closer follow-up or more aggressive treatment of cervical abnormalities. As part of the risk factor identification, we showed the importance of RLU in addition to the presence of HR-HPV. Further studies on the utility of RLU should be done, but this is another promising piece of evidence to show which patients need closer follow-up. Finally, we showed that only

approximately 24% of those infected with HR-HPV were infected with either 16 or 18. This implies that in HIV-infected women the vaccine subtypes may need to be broadened.

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TABLES

Table 1. Baseline characteristics of HIV positive patients in the "HPV Sentinel Surveillance Study and High Risk HPV Prevalence Study" stratified by HPV status.

Characteristics	All patients (n= 486)	HR-HPV prevalence (n=219)
Ethnicity		
Hispanic	60 (12.3%)	25 (41.7%)
Non-Hispanic	423 (87%)	194 (45.9%)
Unknown	3 (0.6%)	n/d^
Race		
White	88 (18.1%)	32 (36.4%)
African American	318 (65.6%)	154 (48.4%)
Hispanic	60 (12.4%)	25 (41.7%)
Asian	6 (1.2%)	2 (33.3%)
Other	9 (1.9%)	6 (66.7%)
Unknown	5 (1%)	n/d
Age Group		
18-29	92 (18.9 %)	52 (56.5%)
30-39	193 (39.7%)	91 (47.2%)
40-49	152 (31.3%)	57 (37.5%)
50-65	48 (9.9%)	19 (39.6%)
Unknown	1 (0.2%)	n/d
History of abnormal Pap		
Yes	284 (58.4%)	146 (51.4%)
No	202 (42.6%)	73 (36.1%)
History of treatment on cervix		
Yes	199 (41%)	95 (47.7%)
No	287 (59%)	124 (43.2%)
City		
MAS	42 (8.6%)	15 (35.7%)
BAL	139 (28.6%)	58 (41.7%)
NOR	196 (40.3%)	101 (51.5%)
DEN	80 (16.5%)	33 (41.3%)
LAX	23 (4.7%)	9 (39.1%)
SEA	6 (1.2%)	3 (50%)
HIV viral load		
Undetectable	200 (41.2%)	80 (40%)
<10,000 copies	115 (23.7%)	50 (43.5%)
≥10,000 copies	171 (35.2%)	89 (52%)
CD4 count		
<50	25 (5.1%)	17 (68%)
50-200	75 (15.4%)	52 (69.3%)
≥200	386 (79.4%)	150 (38.9%)
Antiretroviral use‡		
Yes	274 (56.4%)	135 (49.3%)
No	206 (42.3%)	83 (40%)
Unknown	5 (1%)	1 (20%)
Current smoker		
Yes	219 (45.1%)	117 (44.2%)
No	265 (54.5%)	101 (46.1%)
Unknown	2 (0.4%)	1 (50%)

Parity		
Nulliparious	47 (9.7%)	17 (36.2%)
Primi/Multiparious	400 (82.3%)	185 (46.3%)
Unknown	39 (8%)	17 (43.6%)
Presence of another STI*		
Yes	17 (3.5%)	9 (52.9%)
No	469 (96.5%)	210 (44.8%)
HC2 RLU		
<20	382 (78.6%)	128 (33.5%)
≥20	89 (18.3%)	82 (92.1%)
Unknown	15 (3.1%)	9 (60%)
HPV type		
6	9 (1.9%)	--
11	6 (1.2%)	--
16		21 (9.6%)
18		32 (14.6%)
52		39 (17.8%)
53		40 (18.6%)
68		24 (11%)
70		39 (17.8%)
Number of HR-HPV Types		
1		122 (55.7%)
2		51 (23.3%)
3		25 (11.4%)
4		8 (3.7%)
5		8 (3.7%)
6		4 (1.8%)
7		1 (0.5%)
Cytology		
Normal	287 (59.1%)	77 (26.8%)
ASC-US	74 (15.2%)	36 (48.6%)
ASC-H	2 (0.4%)	2 (100%)
LSIL	91 (18.7%)	80 (87.9%)
HSIL	21 (4.3%)	16 (76.2%)
Unknown	11 (2.3%)	5 (45.5%)
Age at First Sex		
<14	88 (18.1%)	35 (39.8%)
≥14	388 (79.8%)	184 (47.4%)
Unknown	10 (2.1%)	5 (50%)
Lifetime Male Sex Partners		
0	0 (0%)	0 (0%)
1	20 (4.1%)	9 (45%)
2	34 (7%)	16 (47.1%)
3-5	132 (27.2%)	64 (48.5%)
6-10	115 (23.7%)	52 (45.2%)
>10	158 (32.5%)	67 (42.4%)
Unknown	27 (5.6%)	11 (40.7%)

*Sexually transmitted infection (STI)- including Chlamydia and genital herpes
†Antiretroviral use- defined as currently taking any antiretroviral medication
^n/d- not done

Figure 1. Frequency of HR-HPV types among those with HR-HPV infection.

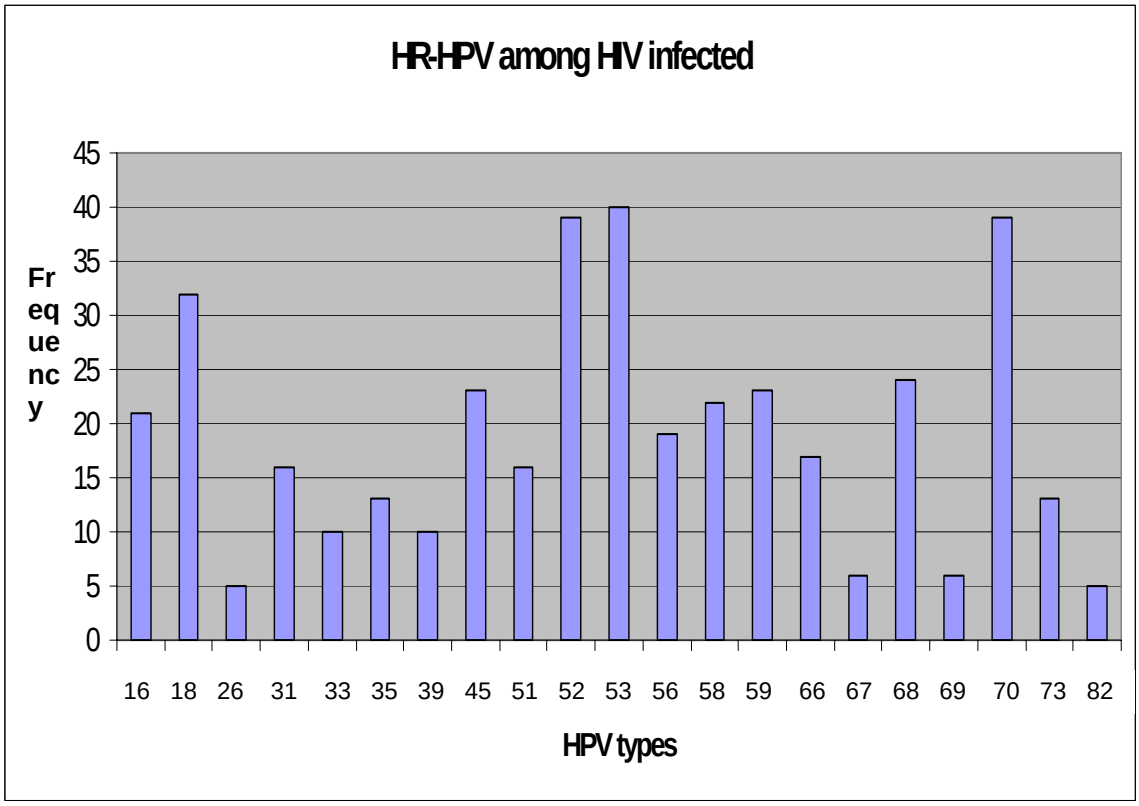

Figure 2. Frequency of HR-HPV types among Pap smear strata.

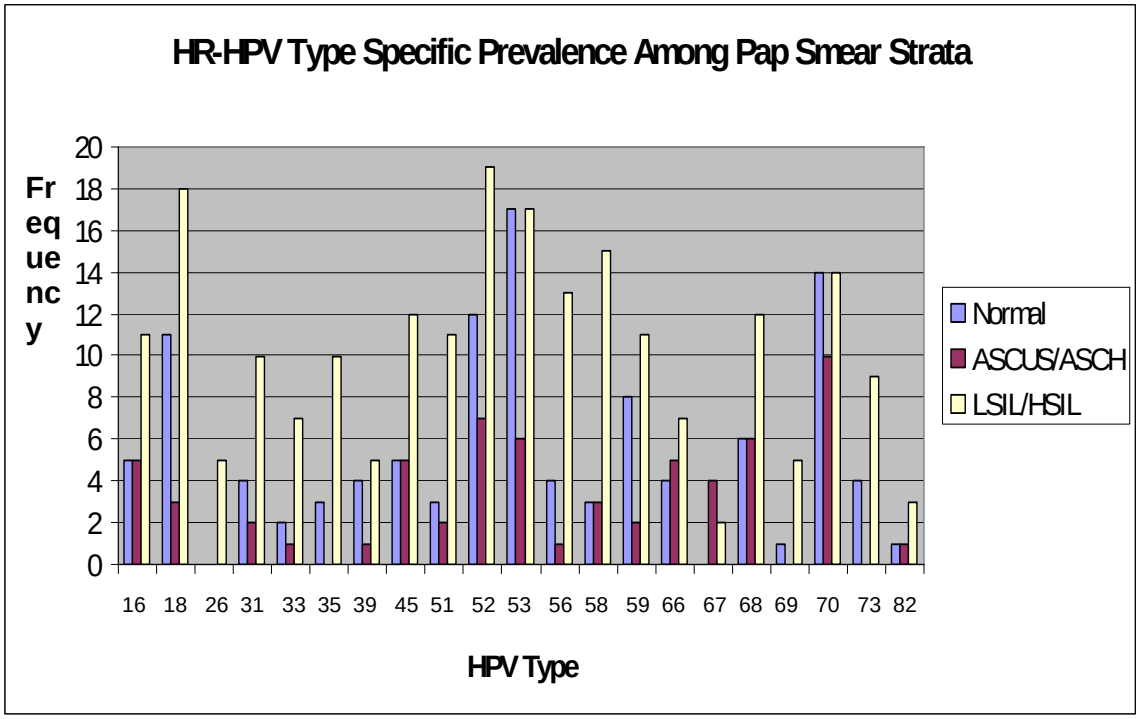

Table 2. Association of characteristics and abnormal Pap smear.

Characteristics	Odds Ratio	95% Confidence Intervals
Race Non-white White*	1.30	0.80, 2.13
Age Group ≥30 <30*	0.93	0.58, 1.48
History of abnormal Pap Yes No*	4.09	2.70, 6.20
History of treatment on cervix Yes No*	1.98	1.36, 2.88
HIV viral load ≥10,000 <10,000*	1.49	1.02, 2.19
CD4 count <200 ≥200*	3.98	2.49, 6.36
Antiretroviral use Yes No*	1.98	1.35, 2.92
Current Smoker Yes No*	0.81	0.56, 1.17
Parity Primi/Multiparious Nulliparious*	1.44	0.74, 2.8
Presence of another STI Yes No*	1.59	0.58, 4.32
Hybrid Capture/PCR Any high risk type Negative*	7.4	4.89, 11.21
RLU ≥20 <20*	14.2	7.57, 26.7
HR-HPV type 16/18/52/53/70 Non-16/18/52/53/70*	4.16	2.74, 6.32
Number of HR-HPV types 2-6 1*	3.47	1.90, 6.33
Age at First Sex <14 ≥14*	0.83	0.51, 1.35

Lifetime Male Sex Partners		
>2	2.28	1.18, 4.39
0-2*		

* Denotes referent group

Table 3A. Comparison of RLU cutoffs with Pap smear results among those with HR-HPV

RLU result	Normal Pap smear	Abnormal Pap smear
<20*	70 (55.6%)	56 (44.4%)
20-499	8 (20.5%)	31 (79.5%)
≥ 500	0	41 (100%)

$p<0.0001$
*referent group

Table 3B. Comparison of those with or without HR-HPV with different RLU values

Stratification	Normal Pap smear	Abnormal Pap smear	RR (95% CI)
HR-HPV with RLU ≥ 20	8 (10%)	72 (90%)	55.2 (23.5-129.5)
HR-HPV with RLU < 20	72 (53.7%)	62 (46.3%)	5.28 (3.03-9.21)
Low risk HPV only	69 (71%)	28 (28.9%)	2.49 (1.33-4.63)
No HPV*	141 (86%)	23 (14%)	--

*referent group

Table 4A. Multivariate risk factor analysis for abnormal Pap smear.

Characteristic	Odds Ratio (95% CI)	p-value
History of Abnormal Pap	**3.1** (1.9-5.1)	<0.0001
CD4 count<200	**1.81** (1.0-3.2)	0.04
Antiretroviral use	**1.64** (1.01-2.66)	0.04
HR-HPV with RLU ≥ 20	**41.78** (17.1-101.9)	<0.0001
HR-HPV with RLU<20	**4.83** (2.7-8.7)	<0.0001
Low risk HPV	**2.27** (1.2-4.4)	0.01

Table 4B. Multivariate risk factor analysis for abnormal Pap smear among those with HR-HPV infection.

Characteristic	Odds Ratio (95% CI)	p-value
Antiretrovirals use	2.45 (1.19-5.05)	0.02
RLU≥20	7.34 (3.01-17.89)	<0.0001
CD4 count <200	2.52 (1.10-5.82)	0.03
History of abnormal Pap	3.38 (1.65-6.92)	0.001
Infection with >1 high risk HPV type	2.55 (1.23-5.31)	0.01

Table 4C. Multivariate risk factor analysis for abnormal Pap smear among those with HR-HPV infection and CD4 count < 200.

Characteristic	Odds Ratio (95% CI)	p-value
History of abnormal Pap	4.54 (1.60-12.93)	0.005
Low risk HPV infection	4.16 (1.64-10.56)	0.003

Table 4D. Multivariate risk factor analysis for abnormal Pap smear among those with HR-HPV infection and CD4 count ≥ 200.

Characteristic	Odds Ratio (95% CI)	p-value
Antiretroviral use	2.78 (1.17-6.64)	0.02
History of Abnormal Pap	3.06 (1.29-7.29)	0.01
RLU≥20	14.32 (4.32-47.42)	<0.0001
Infection with >1 high risk HPV type	3.04 (1.28-7.21)	0.01